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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/822,627	04/12/2004	Jianbo Xie	141-400	3299

47888 7590 09/30/2008

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EXAMINER	
KARPINSKI, LUKE E	
ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
09/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/822,627	XIE ET AL.	
	Examiner	Art Unit	
	LUKE E. KARPINSKI	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-17 and 20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-17 and 20-24* is/are rejected.

7)☐ Claim(s) *8 and 12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/7/2008 has been entered.

Claims

Claims 2-6, 18-19, and 25-33 have been canceled.

Claims 1 and 17 have been amended.

Claims 1, 7-17, and 20-24 are currently pending and under consideration in this action.

Claim Objections

Claim 8 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 8 adds no limitations that are not already found within instant claim 1.

Claim 12 is objected to because of the following informalities: Applicant recites "degrade at a pH of about 11 to about a pH of 12". The grammar in this claim seems strange. The examiner suggests that the second 'about' be moved to between 'of' and '12'.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10, 12, 13, and 14 are rejected under 35 USC 112. Claim 10 recites the limitation "first enteric coating agent". There is insufficient antecedent basis for this limitation in the claim. Claim 1 states only “first enteric coating”. The examiner suggests that the word “agent” be inserted into claim 1 after “first enteric coating”, in order to overcome this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1, 7-17, and 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,160,742 to Mazer et al. in view of US Patent No. 6,372,255 to Saslawski et al. and in further view of US Patent No. 5,478,577 to Sackler et al. and US Patent No. 4,610,870 to Jain et al.

Applicant Claims

Applicant claims an oral pharmaceutical comprising: (a) a core consisting of: oxycodone or a salt thereof, a diluent, and a binder, optionally a glidant, and optionally a lubricant, (b) a delayed release coating consisting essentially of: (i) a pH dependant material consisting of 2 enteric agents; (ii) an inert processing aid and; (iii) optionally a

plasticizer and; (c) an immediate release drug layer comprising: (i) oxycodone or a salt thereof; (ii) a binder; and (d) optionally a cosmetic coating.

Applicant further claims specific types and compounds as excipients, viscosities, pH dissolution values, ratios and, percentages.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Mazer et al. teach a formulation comprising: (a) a core comprising an analgesic (col. 6, lines 65-68), a diluent, specifically maltose, and a binder, specifically PVP (col. 7, lines 11-45); and (b) a delayed release coating consisting essentially of: 30-80% of a pH dependant material consisting of a first enteric agent that begins to dissolve or degrade at a pH of about 5 to 7 (Eudragit L100) and a second enteric agent that begins to dissolve at a pH of above 7 (Eudragit S100) (col. 8, lines 39-42), as evidenced by the "Handbook of Pharmaceutical Excipients" pages that were provided by the Applicant in the Arguments/Remarks filed 12/19/2007, about 20-70% of an inert processing aid (talc); and a plasticizer (acetyltri-n-butyl citrate) (col. 8, lines 43-51).

Mazer et al. also teach about 35-70% of a pH dependant material (Eudragit) (col. 11, lines 13-21). The percentage of Eudragit present is extrapolated from the second coating material taught in col. 11, lines 13-21, the coating material comprises 15% plasticizer and 30% processing aid, the only other ingredient named is the pH dependant material, which means that the pH dependant material is present at 45%. Mazer et al. also teach that said enteric agents are found at a ratio between 1:5 and 5:1 (col. 8, lines 39-42). Mazer et al. also teach said core comprising a binder (PVP) (col. 7,

lines 11-15), a diluent (dextrose) (col. 7, lines 11-26), a glidant and a lubricant (lactose) (col. 7, lines 11-25). Mazer et al. further teach an osmopolymer (polyvinylpyrrolidone) as said binder (col. 7, lines15-30).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Mazer et al. do not teach a single delayed release coating surrounding a core. However, Mazer et al. do teach that each coating has different dissolution properties and are applied separately.

Mazer et al. do not teach an immediate release drug layer. This deficiency in Mazer et al. is cured by Saslawski et al. Saslawski et al. teach an immediate release drug layer comprising an analgesic or a salt thereof (col. 2, lines 54-56) and at least one excipient (col. 5, lines 59-67), said immediate release drug layer covering a sustained release drug layer (abstract). Saslawski et al. also teach the benefit of instant bioavailability and optimization of the supply of the active (col. 1, lines 6-50).

Mazer et al. also do not teach the enteric agents present at a ratio from about 1:2 to 1:4 as claimed in claim14. However, Mazer et al. do teach a ratio of 3:1 and that each enteric agent has different dissolution at designated pH levels.

Mazer et al. also do not teach a single coating comprising enteric agents that begin to dissolve at a pH of above 9 or 11-12 as claimed in claims 12, 21, and 22. However, Mazer et al. do teach a separate coating comprising zein, as well as the fact

that coatings comprising zein lower the amount of active released due to simulated gastric fluids (col. 15, lines 23-50 and figure 1).

Neither Mazer et al. nor Saslawski et al. teach the utilization of oxycodone. This deficiency is cured by Sackler et al. Sackler et al. teach that oxycodone is an analgesic capable of use in the sustained release layer and immediate release layer of a pharmaceutical formulation (col. 6, line 24 to col. 7, line 10).

None of Mazer et al., Saslawski et al., or Sackler et al. explicitly recite said binder having a viscosity of greater than 50,000 or 75,000 mPa when tested in a 2% aqueous solution at 20ºC as claimed in claims 17 and 20. This deficiency is cured by Jain et al. Jain et al. teach binders utilized in the core of a sustained release formulation (abstract), having a viscosity of greater than 75,000 mPa when tested in a 2% aqueous solution at 20ºC, specifically Methocel K-100M (col. 9, table III). Jain et al. also teach that said binders are utilized to obtain a zero order release rate (col. 5, lines 5-15).

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the sustained release coating of Mazer et al. by coating the core with a single delayed release coating in order to produce the invention of instant claims 1 and 17.

One of ordinary skill in the art would have been motivated to do this because Mazer et al. teach that each layer and each component within each layer have different dissolution properties. Therefore it would have been obvious to modify the components within each layer and not apply the second layer in order to provide the desired release kinetics for said active.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to coat the sustained release drug formulation of Mazer et al. with an immediate release drug layer comprising: an analgesic active and an excipient, as taught by Saslawski et al. in order to produce the invention of instant claims 1 and 17.

One of ordinary skill in the art would have been motivated to do this because Mazer et al. teach sustained release drugs and Saslawski et al. teach that covering sustained release drugs with an immediate release layer ensures instant bioavailability followed by a sustained release period, as well as, the fact that formulations with such layers make it possible to optimize the supply of active ingredients in the body. Therefore it would have been obvious to utilize the immediate release layer of Saslawski et al. comprising: an analgesic active and an excipient, with the formulations of Mazer et al. in order to provide instant bioavailability of an active followed by prolonged release of said active.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize oxycodone as an active in the combined

compositions of Mazer et al. and Saslawski et al. in order to produce the invention of instant claims 1 and 17.

One of ordinary skill in the art would have been motivated to do this because both Mazer et al. and Saslawski et al. teach pharmaceutical formulations comprising an analgesic and Sackler et al. teach a formulation comprising oxycodone, as an analgesic, within both an immediate release layer and a sustained release layer of a pharmaceutical formulation. The criticality of the formulations of Mazer et al. and Saslawski et al. lies in the release of an active agent not in the active agent itself. Therefore it would have been obvious to utilize oxycodone as one analgesic of choice in both the sustained release compositions of Mazer et al. and the immediate release compositions of Saslawski et al. in order to provide immediate and prolonged pain relief.

Regarding claims 1, 17, and 20 it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize a binder having a viscosity of over 75,000 mPa when tested in a 2% aqueous solution at 20ºC, specifically Methocel K-100M, in the core formulations of Mazer et al. as taught by Jain et al.

One of ordinary skill in the art would have been motivated to do this because Mazer et al. teach a pharmaceutical core formulation comprising: an active in a matrix with a binder. Jain et al. teach Methocel K-100M as a binder used in the core of sustained release pharmaceuticals. Therefore it would have been obvious to utilize Methocel K-100M in the formulations of Mazer et al. as a binder in order to help achieve zero order release kinetics.

Regarding claim 14, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize a ratio of a first enteric agent and a second enteric agent from about 1:2 to 1:4 in the formulations of Mazer et al.

One of ordinary skill in the art would have been motivated to do this because Mazer et al. teach a ratio of 3:1 and that each enteric agent has different dissolution properties at designated pH levels. Therefore it would have been obvious to modify the enteric agent ratio in order to release more or less active in different sections of the gastrointestinal tract.

Regarding claims 11, 12, 21, and 22, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize zein, which begins to dissolve at a pH of about 11-12, and another enteric agent in a single sustained release layer in the formulations of Mazer et al.

One of ordinary skill in the art would have been motivated to do this because Mazer et al. teach that zein and other enteric agents, in combination, reduce the amount of active released in the stomach and regulate the release within the intestines. One would also be motivated to combine the zein and another enteric agent into a single coating to reduce the number of processing steps during manufacture. Therefore, it would have been obvious to use zein and another enteric agent (Eudragit) in a single coating to speed up manufacture and to produce a formulation which reduces active agent release in the stomach and provides targeted release in different areas of the intestine. It is well known in the art to utilize different components and mixtures thereof for coatings in order to modify where a drug is released in the digestive tract and at

what rate said release occurs. All of the components in the instant application have been taught in the prior art, utilized in combination, as enteric coatings. It would have been obvious to simply incorporate a secondary coating into a primary coating.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments with respect to claims 1, 7-17, and 20-24 have been considered but are moot in view of the new ground(s) of rejection. Any arguments which pertain to the new rejection will be answered below.

Applicant argues that Mazer et al. is not directed toward analgesic drugs and does not teach the utilization of oxycodone.

This argument is not found persuasive because Mazer et al. is directed to analgesic drugs (col. 6, lines 65-68) and Sackler et al. is utilized to teach that oxycodone is an analgesic that is can be utilized in delayed and immediate release formulations.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections

are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant argues that the dosage forms of Mazer et al. do not contain an immediate release layer of oxycodone.

This argument is not found persuasive because the lack of an immediate release layer in Mazer et al. is cured by Saslawski et al. and the lack of oxycodone is cured by Sackler et al. as described above in the 103 rejection.

Applicant also argues that the references do not rely primarily upon pH dependant agents and that the cited references do not disclose the combination of two pH dependant agents.

This argument is not found persuasive. Although the references may not rely primarily on pH dependant agents the references do teach that pH dependant agents may be utilized to control the release of active pharmaceuticals. Further, Mazer et al. to teach the utilization of two pH dependant agents in combination (col. 8, lines 39-42), Eudragit L100 and Eudragit S100 are both pH dependant agents.

Applicant also argues that Saslawski et al. also teach opioid release independently of pH.

This argument is not persuasive because Saslawski et al. is relied upon to teach that an instant release coating may be utilized over a delayed release coating and Mazer et al. is utilized to teach the enteric coatings.

Applicant also argues that one could not just apply the coating systems of Mazer et al. and that said coating systems would have to be modified.

This argument is not found persuasive. Although Mazer et al. do not explicitly disclose the coating system of the present invention, as a single layer comprising two different enteric agents, Mazer et al. do teach all of the claimed components. Mazer et al. may teach additional layers over the claimed layer, however, it was well within the skill of one of ordinary skill in the art to recognize that not all layers of Mazer et al. are necessary and that one could modify the release properties of said coating system by utilizing only one of the layers, or through the combination of the components of both layers into a single layer.

Conclusion

Claims 2-6, 18-19, and 25-33 have been canceled.

Claims 1 and 17 have been amended.

Claims 1, 7-17, and 20-24 are rejected.

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LUKE E. KARPINSKI whose telephone number is (571)270-3501. The examiner can normally be reached on Monday Friday 9-5 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LEK

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